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10/539,107	06/15/2005	Tomasz Heyduk	102364	2295

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,107	HEYDUK ET AL.	
	Examiner	Art Unit	
	NARAYAN K. BHAT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109-117 and 119-130* is/are pending in the application.

4a) Of the above claim(s) *112-115,117 and 128-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,109,116 and 119-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This office action is written in reply to applicant's correspondence filed December 31, 2008. Claims 109, 119 and 127 were amended. Claim 118 was cancelled. Applicant's amendments requiring a non-nucleic acid flexible linker necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**.

Status of the Claims

2. Claims 109-117 and 119-130 are pending in this application.

3. Claims 112-115, 117 and 128-130 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) in the reply filed on April 16, 2007.

4. Applicant's arguments filed on December 31, 2008 have been thoroughly reviewed and are addressed following the rejections.

5. Claims 109-111, 116 and 119-127 are under examination.

Amendments to the Claims

6. Amendments to the claims 109, 119 and 127 are reviewed and entered.

Declarations

7. The declaration under 37 CFR 1.132 filed by Dr. Heyduk on December 31, 2008 to highlight the higher sensitivity of the claimed sensor relative to that of Baez et al is noted. However, as discussed below, the declarations and support documents provided are not enough to overcome the 102(b) rejections set forth in this office action.

Dr. Heyduk calculated the free energy for association using HYTHER program at 20^0 C, which is not commensurate in scope with the claimed range of about 21 to about 40^0 C. Dr. Heyduk also provided data for free energy of association at 1M salt concentration, which also is not commensurate in scope with the claimed range of about 1 mM to about 100 mM. Furthermore, using HYTHER program, the free energy of association of Baez sequence (CGCCCGA) at 50 mM salt concentration at a temperature of 37^0 C (which commensurate in scope with the claimed range of temperature and salt concentration) is 6.05 kcal/mol. Hence the sensor of Baez et al is within the range from about 5.5 kcal/mole to about 8.0 kcal/mole as claimed.

Dr. Heyduk also shows that a sensor having the free energy association between about 5.5 kcal/mol and about 8.0 kcal/mole provides a robust signal, whereas sensor having higher than 8.0 kcal/mol did not produce signal (Declaration pg. 2). Dr. Heyduk asserts that the example provides a comparison between the claimed sensor and that of Baez et al. However as noted as above, the example provided in the December 31, 2008 supporting document is not commensurate in scope with the claim. Therefore the example cannot compare the claimed sensor to that of Baez et al as asserted. The sensor of Baez et al has the structural components of the sensor including free energy of association in the claimed range, and non-nucleic acid linker. Therefore, the declarations and the supporting documents provided are not sufficient to overcome the rejections set forth in this office action.

Note to Applicants

8. The information disclosure statement filed December 31, 2008 is considered However, it is noted that 20030110739, incorrectly cites Heyduk. The true inventor for PGPUB is Sass.

Objection

9. The claim listing includes the text of cancelled claim 118. No claim text should be presented for any claim in the claim listing with the status of "canceled" (See MPEP, 714 [R6] (4) for further details).

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 109-111, 116, 119-122 and 124-127 are rejected under 35 U.S.C. 102(b) as being anticipated by Baez et al (USPGPUB NO. 2002/0051986 published May 2, 2002) as evidenced by HYTHER program.

Previous rejections are maintained and additional claim limitation of amended claims are discussed below.

Note: Claims have been interpreted based on structural components in the claim (MPEP 2114).

Regarding claim 109, Baez et al teaches a molecular biosensor having two nucleic acids constructs with the claimed structural components as discussed below.

Regarding structural component R1, Baez et al teaches nucleic acid reporter conjugate A comprising a first antibody (i.e., R1) binding to a first epitope on a target molecule (Fig. 1, first Antibody - shown as lambda shape in A, Target B, first Epitope C1 paragraphs 0017, 0023 and 0089).

Regarding structural component R5, Baez et al teaches nucleic acid reporter conjugate A1 comprising a second antibody (i.e., R5) binding to a second epitope on a target molecule (Fig. 1, second Antibody – shown as lambda shape in A1, Target B, second Epitope C2, paragraphs 0017, 0023 and 0089).

Regarding structural component R2, Baez et al teaches non-nucleic acid linkers SATA-Sulfo and SMCC (i.e., R2) to attach the first antibody (i.e., R1) to nucleic acid D1 (i.e., R3, paragraphs 0089 and 0165-0174).

Regarding structural component R6, Baez et al teaches non-nucleic acid SATA-Sulfo and SMCC linker (i.e., R6) to attach the second antibody (i.e., R5) to nucleic acid D2 (i.e., R7, paragraphs 0089 and 0165-0174).

Regarding structural components R3 and R7, Baez et al further teaches that nucleic acid in nucleic acid reporter conjugates A and A1 further comprises oligonucleotide T66 (i.e., R3, Table 1) and oligonucleotide T68 (i.e., R7, Table 1) and have seven base pair complementary region at the 3' end and have a sequence CGCCCGA (Fig. 3, Second panel from the top, Table 1, paragraphs 0182-0183). Baez et al also teaches a temperature of 37C (paragraph 0184) and salt concentration of 50

mM (paragraph 0190). A temperature of 37C is within the range from about 21C to about 40C as claimed. A salt concentration of 50 mM is within the range of about 1 mM to about 100 mM as claimed.

A sequence comprising CGCCCGA, at 50 mM salt concentration and at a temperature of 37C has a free energy of association of 6.05 kcal/mol, which is in the range from about 5.5 kcal/mole to about 8.0 kcal/mole as claimed (Free energy association –HYTHER document). It is noted that the reference of HYTHER program for calculating free energy is used only to confirm the known fact in the art of free energy of association of complementary nucleotide sequences.

Regarding structural components R4 and R8, Baez et al teaches that the nucleic acid reporter conjugate A comprises fluorophore A (i.e., R4) and nucleic acid reporter conjugate A1 comprises fluorophore B (i.e., R8, paragraph 0139). Baez et al also teaches that binding of nucleic acid reporter conjugates A and A1to an analyte brings the complementary sequences of the R3 and R7 into proximity to produce analyte dependent reporter complex, resulting in fluorescent energy transfer from fluorophore A to fluorophore B causing a shift in the emission spectrum thereby detecting the analyte (paragraphs 0137-0139, 0183). The nucleic acid reporter conjugate A of Baez et al is the nucleic acid construct comprising R1-R2-R3-R4 and the nucleic acid reporter conjugate A1 of Baez et al is the nucleic acid construct comprising R5-R6-R7-R8 as claimed.

Regarding claim 110, Baez et al teaches that the target molecule is selected from the group consisting of an analyte, a protein, a polypeptide, a nucleic acid, a

biomolecule, a macromolecular complex and a microbial organism (paragraphs 0050 and 0052).

Regarding claim 111, Baez et al teaches that the target molecule is a protein or polypeptide (paragraph 0052).

Regarding claim 116, Baez et al teaches that the R1 and R5 are each antibodies (paragraphs 0017 and 0183).

Regarding claims 119 and 120, as described above, Baez et al teaches that the first antibody (i.e., R1) is covalently coupled to T66 nucleic acid molecule (i.e., R3) with SATA and SMCC linkers (i.e., R2) and the second antibody (i.e., R5) is covalently coupled to T68 nucleic acid molecule (i.e., R7) with SATA and SMCC linkers (i.e., R6, paragraphs 0165-174, 0183). The free energy of the formed bond is interpreted broadly as an obvious variant of the molecular sensor taught by Baez et al.

Regarding claim 121, as described above Baez et al teaches SATA and Sulfo-SMCC bifunctional chemical crosslinker (I.e., R2 and R6) to couple antibodies to nucleic acid molecules (paragraphs 0165 -0174).

Regarding claim 122, Baez et al teaches a Sulfo-SMCC bifunctional chemical crosslinker (paragraphs 0165 and 0169). Sulfo-SMCC bifunctional chemical crosslinker has a length of 11.9 angstrom as taught by Uptima brochure (pg. 2, paragraph 4). It is noted that the reference of Uptima brochure is used only to confirm the known fact in the art of linker length. It is also noted that the claim recitation of R2 and R6 from Zero to 500 angstrom in length, indicates that R2 and R6 are not needed when the length of the bifunctional cross linker is zero angstrom.

Regarding claim 124, Baez et al teaches that the R3 and R7 are seven nucleotide in length (paragraph 0183), which is within the range from about 4 to about 15 nucleotide in length as claimed.

Regarding claim 125, Baez et al teaches that the nucleic acid reporter conjugate A comprises fluorophore A (i.e., R4) and nucleic acid reporter conjugate A1 comprises fluorophore B (i.e., R8) that transfer energy producing a detectable signal (paragraph 0139).

Regarding claim 126, Baez et al teaches FRET (paragraph 0139).

Regarding claim 127, Baez et al teaches a molecular biosensor having two nucleic acids constructs with the claimed structural components as discussed below.

Regarding structural component R1, Baez et al teaches nucleic acid reporter conjugate A comprising a first antibody (i.e., R1) binding to a first epitope on a target molecule (Fig. 1, first Antibody - shown as lambda shape in A, Target B, first Epitope C1 paragraphs 0017, 0023 and 0089). It is noted that the claims are interpreted based on structural components of the sensor and not on the intended use of the sensor (MPEP 2114). The type of target molecule does not further define the structure of the sensor. However, the sensor of Baez et al does detect nucleic acid segments (paragraph 0052).

Regarding structural component R5, Baez et al teaches nucleic acid reporter conjugate A1 comprising a second antibody (i.e., R5) binding to a second epitope on a target molecule (Fig. 1, second Antibody – shown as lambda shape in A1, Target B, second Epitope C2, paragraphs 0017, 0023 and 0089).

Regarding structural component R2, Baez et al teaches non-nucleic acid linkers SATA-Sulfo and SMCC (i.e., R2) to covalently attach the first antibody (i.e., R1) to nucleic acid D1 (i.e., R3, paragraphs 0089 and 0165-0174).

Regarding structural component R6, Baez et al teaches non-nucleic acid SATA-Sulfo and SMCC linker (i.e., R6) to covalently attach the second antibody (i.e., R5) to nucleic acid D2 (i.e., R7, paragraphs 0089 and 0165-0174). Sulfo-SMCC bifunctional chemical crosslinker has a length of 11.9 angstrom as taught by Uptima brochure (pg. 2, paragraph 4). It is noted that the reference of Uptima brochure is used only to confirm the known fact in the art of linker length. It is also noted that the claim recitation of R2 and R6 from Zero to 500 angstrom in length, indicates that R2 and R6 are not needed when the length of the bifunctional cross linker is zero angstrom.

Regarding structural components R3 and R7, Baez et al further teaches that nucleic acid in nucleic acid reporter conjugates A and A1 further comprises oligonucleotide T66 (i.e., R3, Table 1) and oligonucleotide T68 (i.e., R7, Table 1) and have seven base pair complementary region at the 3' end and have a sequence CGCCCGA (Fig. 3, Second panel from the top, Table 1, paragraphs 0182-0183). Baez et al also teaches a temperature of 37C (paragraph 0184) and salt concentration of 50 mM (paragraph 0190). A temperature of 37C is within the range from about 21C to about 40C as claimed. A salt concentration of 50 mM is within the range of about 1 mM to about 100 mM as claimed.

A sequence comprising CGCCCGA, at 50 mM salt concentration and at a temperature of 37C has a free energy of association of 6.05 kcal/mol, which is in the

range from about 5.5 kcal/mole to about 8.0 kcal/mole as claimed (Free energy association –HYTHER document). It is noted that the reference of HYTHER program for calculating free energy is used only to confirm the known fact in the art of free energy of association of complementary nucleotide sequences.

Regarding structural components R4 and R8, Baez et al teaches that the nucleic acid reporter conjugate A comprises fluorophore A (i.e., R4) and nucleic acid reporter conjugate A1 comprises fluorophore B (i.e., R8, paragraph 0139). Baez et al also teaches that binding of nucleic acid reporter conjugates A and A1to an analyte brings the complementary sequences of the R3 and R7 into proximity to produce analyte dependent reporter complex, resulting in FRET from fluorophore A to fluorophore B causing a shift in the emission spectrum thereby detecting the analyte (paragraphs 0137-0139, 0183). The nucleic acid reporter conjugate A of Baez et al is the nucleic acid construct comprising R1-R2-R3-R4 and the nucleic acid reporter conjugate A1 of Baez et al is the nucleic acid construct comprising R5-R6-R7-R8 as claimed.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 109 and 123 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Baez et al (USPGPUB NO. 2002/0051986 published May 2, 2002) as evidenced by HYTHER program in view of Zalipsky (Advanced Drug Delivery Reviews, 1995, 16, 157-182).

Claim 123 is dependent from claim 109. The teachings of Baez et al regarding claim 109 are described above in section 11.

Regarding claim 123, Baez et al teaches that sensor comprises non-nucleic acid linker (i.e., R2 and R6, paragraph 0169) but is silent about polyethylene glycol. However polyethylene glycol was known at the time of the claimed invention was made as taught by Zalipsky, who teaches polyethylene glycol linker to conjugate a variety of ligands (Fig. 1, Table 1) and further teaches that the linker increased stability and solubility of the polyethylene glycol conjugate (Table 1, see comments section). Zalipsky also teaches polyethylene glycol has a molecular weight of 1000 daltons and has a general structure of HO-(CH2-CH2O)n –CH2-CH2-OH thus teaching the n value of about 23 (pg. 158, column 2, paragraph 2). Wikipedia brochure teaches that C-C bond length is 1.54 angstrom and C-O bond length is 1.43 angstrom (See the brochure). Polyethylene

glycol with 1000 molecular weight has the length of about 70 angstrom unit (C-C bond length 1.54 angstrom + C-O bond length 1.43 angstrom; polyethylene glycol 1000 = 23 (1.54+ 1.43)=~ 70 angstrom unit). It is noted that Wikipedia brochure is used to confirm the known fact about the C-O and C-C bond length. The polyethylene glycol taught by Zalipsky of 70 angstrom length is within the claimed range from zero to 500 angstrom in length. It is also noted that the claimed range of Zero to 500 angstrom encompasses a length, whereby R2 and R6 are not present when the length is zero.

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the linker of Baez et al with the polyethylene glycol linker of Zalipsky with a reasonable expectation of success.

An artisan would have been motivated to use the PEG linker in the sensor of Baez et al with the expected benefit of increasing stability and solubility of the polyethylene glycol conjugate as taught by Zalipsky (Table 1, see comments section).

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 109-111, 116, 119-127 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 11/836,339 in view of Baez et al (USPGPUB NO. 2002/0051986 published may 2, 2002). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding instant claims 109 and 127, the claim 1 of copending '339 application is drawn to a molecular biosensor comprising R47-R48-R49-R50 and R51-R52-R53-R54 and has structural features of epitope binding agent (R47 and R51), flexible PEG linkers (R48 and R52), complementary nucleic acid sequences (R49 and R53) and detection means (R50 and R53). Additional structural limitation of flexible linkers, nucleic acid composition and detection means of instant claim 127 are recited in claims 2-6 of the copending '339 application. The molecular biosensor of the claim 1 of copending '339 application differs from the instant claim 1 and 127 molecular biosensor in the epitope binding agent structural features, specifically, R47 epitope binding agent is not an antibody molecule (as required by the instant claim 127) and the other epitope binding agent, R51, does not bind to a target molecule (as required by claim 1 and 127).

However, epitope binding agents binding to the first and second epitope on the target molecule were known in the art at the time of the claimed invention was made as

taught by Baez et al, who teaches the nucleic acid labeled reporter conjugates selectively binding to the two epitopes on the analyte molecule (Fig. 1, Left panel, nucleic acid reporter conjugates, # A and A1, Analyte # B, Epitope binding agents A and A1 binding C1 and C2 epitopes on the analyte, paragraph 0089) and further teaches that epitope binding agents comprise antibodies (Fig. 1, left panel, Example 1, paragraphs 0122, 0182-0183). Baez et al also teaches that binding of two reporter conjugates to the same analyte molecule provides the necessary spatial alignment to enable nucleic acid labels to be joined enzymatically to form an analyte specific amplicons, which greatly enhances the ability to detect analytes at low concentrations (paragraphs 0088-0089).

It would have been obvious to one having the ordinary skill in the art to include nucleic acid constructs with two epitope binding agent for the same target molecule of Baez et al into the claim 1 of the copending '339 application with the expected benefit of binding of two epitope binding agents to the same analyte molecule providing the necessary spatial alignment to enable nucleic acid labels to be joined enzymatically to form an analyte specific amplicons, which greatly enhances the ability to detect analytes at low concentrations as taught by Baez et al (paragraphs 0088-0089 and 0183).

It is also noted that Baez et al further discloses additional limitations required by instant dependent claims 110-111, 116 and 119-126 as described in detail in this office action in section 8. Therefore the embodiments of claims 110-111, 116 and 119-126 are also obvious for the same reasons given above for instant claims 109 and 127.

Dependent claims 110-111, 116 and 119-126 are obvious over claims 1-11 of the '339 copending application in view of Baez et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 109-111, 116, 119-127 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 11/836,333 in view of Baez et al (USPGPUB NO. 2002/0051986 published may 2, 2002). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding instant claims 109 and 127, the claim 1 of copending '333 application is drawn to a molecular biosensor comprising R24-R25-R26-R27 and R28-R29-R30-R31 and has structural features of epitope binding agent (R24 and R28), flexible PEG linkers (R25 and R29), nucleic acid sequences (R26 and R30) and detection means (R27 and R31), wherein epitope binding agents R24 and R28 bind to the first and second epitopes on the target molecule and further comprises of antibody (claim 5 of the copending '333 application, limitations of instant claim 127). Additional structural limitation of flexible linkers, nucleic acid composition and detection means of instant claim 127 are recited in claims 2, 6-8 of the copending '333 application. Biomolecular sensor of claims 1 and 5-8 of copending '333 application differs from the molecular biosensor of instant claim 109 and 127 in that the R26 and R30 nucleic acids are not complementary to each other.

However, nucleic acid structure complementary to each other were known in the art at the time of the claimed invention was made as taught by Baez et al, who teaches the nucleic acid labeled reporter conjugates selectively binding to the two epitopes on the analyte molecule (Fig. 1, Left panel, nucleic acid reporter conjugates, # A and A1, Analyte # B, Epitope binding agents A and A1 binding C1 and C2 epitopes on the analyte, paragraph 0089) and further teaches that A and A1comprise nucleic acid sequences (similar to R26 and R30) and are complementary (Fig. 3, Second panel from the Top, paragraph 0183). Baez et al also teaches that nucleic acid complementary regions serve as extension primers to produce the double stranded DNA to form an analyte specific amplicons, which greatly enhances the ability to detect analytes at low concentrations (paragraphs 0088-0089 and 0183).

It would have been obvious to one having the ordinary skill in the art to include nucleic acid constructs with complementary regions of Baez et al into the claim 1 of the copending '333 application with the expected benefit of providing double stranded DNA to form an analyte specific amplicons, which greatly enhances the ability to detect analytes at low concentrations as taught by Baez et al (paragraphs 0088-0089 and 0183).

It is also noted that Baez et al further discloses additional limitations required by instant dependent claims 110-111, 116 and 119-126 as described in detail in this office action in section 8. Therefore the embodiments of claims 110-111, 116 and 119-126 are also obvious for the same reasons given above for instant claims 109 and 127.

Dependent claims 110-111, 116 and 119-126 are obvious over claims 1-9 of the '333 copending application in view of Baez et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to remarks from the Applicants
Rejections under 35 U.S.C. § 102(b)

18. Applicant's arguments filed December 31, 2008 have been fully considered but they are not persuasive for the following reasons.

Applicants argue that nowhere does the cited art disclose or suggest non-nucleic acid linkers or free energy of association between about 5.5 kcal/mol and about 8.0 kcal/mol (Remarks, pg. 9, last sentence). These arguments are not persuasive because as described above in section 11, Baez et al teaches non-nucleic acid SATA / SMCC linkers (R2 and R6) to conjugate antibodies (R1 or R5) to nucleic acid molecule (R3 or R7). Furthermore, Baez et al teaches that R3 and R7 component of the R1-R2-R3-R4 and R5-R6-R7-R8 sensor have seven base pair complementary region at the 3' end and have a sequence CGCCCGA (Table 1, paragraphs 0182-0183). As described above in section 7, using the HYTHER program (Used by Dr. Heyduk), CGCCCGA sequence at 50 mM salt concentration and at a temperature of 37^0 C has a free energy of association of 6.05 kcal/mol, which is in the range from about 5.5 kcal/mole to about 8.0 kcal/mole as claimed. Therefore arguments are not persuasive because Baez et al teaches the sensor as claimed.

Applicants further argues that the sensor of Baez et al is comprised solely of nucleic acid and that Baez et al fails to disclose a non-nucleic acid linker and free energy of association within the claimed range (Pg. 11, last paragraph). These arguments are not persuasive for the same reasons as described above.

Applicant's remaining arguments are repetitive and further argue elements provided in the declaration by Heyduk (Remarks, pgs. 12 and 13). These arguments are not persuasive for the same reasons as described above. Furthermore, declarations and the supporting documents provided by Dr. Heyduk are not sufficient to overcome the rejections set forth in this office action.

Rejections under 35 U.S.C. § 103(a)

19. Applicant's arguments with respect to claims 109 and 123 have been considered but are not persuasive for the following reasons.

Applicants further reiterate that Baez et al do not teach the free energy of association within the claimed range (pg. 14, second paragraph). These arguments are not persuasive for the same reasons as described above.

Applicants further argue that prima facie case has not established (Remarks, pg. 15). This argument is not persuasive because Applicants have asserted that Zalipsky et al teaches polyethylene glycol linker (Remarks, pg. 15, paragraph 5). The claim recitation of R2 and R6 from Zero to 500 angstrom in length encompasses a length, whereby R2 and R6 are not present when the length is zero. Baez et al and Zalipsky et

al teach the structural components of the sensor as claimed. Therefore arguments are not persuasive.

Applicants further argue that claimed biosensor achieves unexpected results compared to the biosensor of the cited art and therefore request for withdrawal of the obviousness rejection (Remarks, pgs. 16-18). These arguments are not persuasive because as described above in section 7, declarations and the supporting documents provided by Dr. Heyduk are not sufficient to over come the rejections set forth in this office action. Furthermore, example provided to illustrate unexpected results is not commensurate in scope with the claim.

Double Patenting

20. Applicants have not traversed the obviousness-type double patenting rejection. Therefore, provisional obviousness-type double patenting rejection of instant claims 109-111, 116, 119-127 over claims 1-11 of co-pending Application No. 11/836,339 are maintained.

For the reasons as cited above, provisional obviousness-type double patenting rejection of instant claims 109-111, 116, 119-127 over claims 1-8 of copending Application No. 11/836,333 are maintained.

Conclusion

21. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

/BJ Forman/

Primary Examiner, Art Unit 1634